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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/589,152	05/31/2007	David J. Topham	21108.0043U2	5681

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EXAMINER	
HUMPHREY, LOUISE WANG ZHIYING	
ART UNIT	**PAPER NUMBER**
1648	
MAIL DATE	**DELIVERY MODE**
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/589,152	TOPHAM ET AL.	
	Examiner	Art Unit	
	LOUISE HUMPHREY	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-52* is/are pending in the application.

4a) Of the above claim(s) *5-15,17,18,21-27,29,31,35 and 37-52* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,16,19,20,28,30,32-34 and 36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to the amendment filed 08 October 2010.

Claims 1-52 are pending.

Claims 5-15, 17, 18, 21-27, 29, 31, 35 and 37-52 are withdrawn.

Claims 1-4, 16, 19, 20, 28, 30, 32-34 and 36 are currently examined.

WITHDRAWN OBJECTION

The objection to claim 1 and the specification is withdrawn in light of Applicant's amendment.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-4, 16, 19, 20, 28, 30, 32-34 and 36 under 35 U.S.C. §103(a) as being obvious over Braun *et al*. (2003) in view of Novak *et al*. (1999) is maintained.

The instant claims are directed to a method of assessing the efficacy of an immune response to a selected antigen in a subject comprising: (1) introducing into the subject the antigen; (2) collecting a tissue sample from the subject; and (3) detecting the presence of or isolating and quantifying, or measuring, the level of VLA-1^+ antigen-

specific T cells in the sample. Claims 2-4 further limit the antigen to a viral antigen, and particularly, an influenza A antigen. Claim 16 further limits the tissue sample to pulmonary lavage, which reads on bronchoalveolar lavage. Claim 19 further limits he antigen-specific T cells to peripheral memory T cells. Claim 20 further limits the collecting step to take place 6-10 days after the antigen introduction. Claim 28 further limits the subject to a human. Claim 30 further limits the detecting step to the technique of flow cytometry. Claim 32 further limits the method to detecting CD45RO, CD45RA, CD44, CD62L, CD27, and CD43 on the VLA-1+ antigen-specific T cells.

Braun discloses a method of assessing the activity and analyzing surface receptor expression of $CD4^+$ T cells from patients (human subjects) with pulmonary diseases (page 20, left column, middle paragraph), comprising the claimed method steps of (2) collecting from the subjects a tissue sample that is bronchoalveolar lavage and (3) detecting and quantifying the level of VLA-1^+ T cells (page 24, Table 5) and detecting activation markers (page 24, Fig. 2) such as CD45RO, CD62L and CD27 by flow cytometry (page 21, right column, first paragraph). CD45RO is a marker for periphery memory T cells (page 20, left column, middle paragraph). Elevated level of VLA-1 is expressed on $CD103^+/CD4^+$ T cells (Abstract), which level is significantly higher in pulmonary diseases than healthy controls (page 19, left column, last four lines). VLA-1 can be detected weeks after activation (page 19, right column), which reads on the claim limitation of wherein the tissue sample is collected 6-10 days after the antigen introduction.

Braun does not disclose introducing an antigen into the subject before detecting, isolating and measuring the VLA-1^+ antigen-specific T cells.

Novak suggests introducing an influenza A virus antigen into human subjects, collecting a tissue sample and detecting antigen-specific T cells by tetramer staining (page R64, right column, last paragraph) and flow cytometry (page R64, Figure 1b).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Braun's immunity assessment method so as to include the initial step of introducing an influenza A antigen, as suggested by Novak. The skilled artisan would have been motivated to make this modification in order to assess the immune response to any antigen introduced to a subject. There would be a reasonable expectation of success because an influenza A virus infects human lungs and the method of how to assess an immune response in human lungs is already disclosed by Braun. Thus, the invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Arguments

Applicant's arguments have been fully considered but are not persuasive. Applicant argues that the cited art alone or in combination fails to teach or suggest that the presence of VLA-1^+ antigen-specific T cells is indicative of an efficacious immune response and that T cell activation status and efficacy are NOT the same thing. Applicant further argues that the level of VLA-1 is not related to the level of

$CD4^+CD103^+$ cells and that no showing is ever made of the expression of VLA-1 in normal versus diseased individuals. Finally, Applicant reiterated the argument that there is no showing in Braun or Novak to suggest that the VLA-1^+ cells represent a viable pool of immune memory cells. Applicant also argued hindsight reasoning in the Examiner's rationale.

In response to applicant's argument that the efficacy of immune response is not taught or suggested in the cited prior art, it is respectfully submitted that the efficacy of the immune response can be determined by the combination of the presence of antigen-specific T cells, as determined via the administration of the influenza antigen as per the suggestion by Novak, and of the activity of T cells, which is detected by the presence of VLA-1, as per the suggestion of Braun *et al*. The

In response to Applicant's argument regarding the $CD103^+/CD4^+$ T cells and VLA-1 level in the Braun *et al*. reference, it is hereby clarified that Examiner stated in the previous Office action on page 7: "Elevated level of VLA-1 is expressed on $CD103^+/CD4^+$ T cells, which level is significantly higher in pulmonary disease than healthy controls." The word "which" refers to the $CD103^+/CD4^+$ T cells. Therefore, Examiner is not making any assertion that is not based on the disclosure in the Braun *et al*. reference.

In response to Applicant's argument about the lack of showing of VLA-1 expression in normal versus diseased individuals, it is respectfully submitted that the presence of VLA in normal versus diseased lungs is not essential based on the consideration that the method suggested by the present disclosures is specifically

looking for the activation of T cells in response to the introduction of an influenza antigen. Braun expressly discloses that VLA-1 is a marker of T cell activation while Novak expressly suggests introducing an antigen to activate T cells. Therefore, the combination of the Braun and Novak yields the predictable results of measuring T cells that are specifically activated in response to the target antigen/pathogen.

In response to Applicant's argument that there is no suggestion or motivation in any of the cited documents of the use of VLA-1 as indication of an effective immune response, the rationale to modify or combine the prior art does not have to be expressly stated in the prior art; the rationale may be expressly or impliedly contained in the prior art or it may be reasoned from knowledge generally available to one of ordinary skill in the art, established scientific principles, or legal precedent established by prior case law. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958, F2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). See also *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir. 2000) (setting forth test for implicit teachings); *In re Eli Lilly & Co.*, 902 F.2d 943, 14 USPQ2d 1741 (Fed. Cir. 1990) (discussion of reliance on legal precedent); *In re Nilssen*, 851 F.2d 1401, 1403, 7 USPQ2d 1500, 1502 (Fed. Cir. 1988) (references do not have to explicitly suggest combining teachings); *Ex parte Clapp*, 227 USPQ 972 (Bd. Pat. App. & Inter. 1985) (examiner must present convincing line of reasoning supporting rejection); and *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993) (reliance on logic and sound scientific reasoning).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

The rationale of the instant rejection is based on combining prior art elements according to known methods to yield the predictable results of detecting/isolating antigen-specific CD4+ T cells proliferating in response to an antigen such as influenza A HA peptide. The literal recitation of the presence of VLA-1^+ antigen-specific T cells indicating an effective immune response in the subject is not required for establishing a prima facie obviousness case as this method property is an advantage of the prior art method. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Zachariah Lucas, can be reached on 571-272-0905. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/L. H./
Examiner, Art Unit 1648

/Zachariah Lucas/
Supervisory Patent Examiner, Art Unit 1648